

Serial No.: 09/677,653
Filing Date: October 3, 2000

C6 22. An isolated nucleic acid molecule as claimed in claim 21 in which the second sequence is double stranded RNA.

REMARKS

Claims 17, 18, 21, and 22 have been amended. Support for amended claim 17 is found on page 11, line 14. Support for amended claim 18 is found on page 18, lines 19-25. Support for amended claim 21 is found on page 116, lines 6-10. Support for amended claim 22 is found on page 117, lines 5-9. Claims 15-23 are pending in this case. Claim 24 is withdrawn from consideration as directed to a non-elected invention. Amendments to the specification and to the claims are indicated in the section entitled "Versions With Markings to Show Changes Made" and a list of the now pending claims, as amended, is provided in the section entitled "Pending Claims 15-23, as Amended."

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claim 15 (and dependent claims 16-23) stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner maintains that claim 15 is indefinite because the metes and bounds of a "second sequence which is insecticidal" are not clear. Applicant maintains that the term "insecticidal" is well known in the art and refers to the ability of an agent to induce or generate a detrimental effect against an insect. Examples of such detrimental effects include, but are not limited to, a reduction in reproductive rate, reduced feeding and/or development or death of the insect. In addition, the mechanisms for detecting the insecticidal activity of an agent are well known in the art. These mechanisms are illustrated in Examples 9 and 11 of the specification, in which insect development, larval weight, and plant damage are described as determinative of

Serial No.: 09/677,653
Filing Date: October 3, 2000

insecticidal activity. The term, "insecticidal" is moreover, a layman's term, which is defined in Webster's Ninth New Collegiate Dictionary (1986) as pertaining to the destruction or control of insects or to an insecticide. For the foregoing reasons, Applicant respectfully requests withdrawal of the outstanding rejection.

Claim 17 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting "HaSV" without identifying the full name of the virus. Applicant has amended claim 17 to recite a *Helicoverpa armigera* stunt virus. Applicant further notes that it is well known in the art that the terms "*Helicoverpa armigera*" and "*Heliothis armigera*" are interchangeable. Since *Helicoverpa armigera* is the classification most recently adopted for the virus, Applicant has amended claim 17 to recite an isolated nucleic acid molecule in which the insect small RNA virus is *Helicoverpa armigera* stunt virus (HaSV). Applicant accordingly requests withdrawal of the outstanding rejection.

Claim 18 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to identify the full name of the virus and for reciting a protein without providing a sequence identification number. In compliance with the Examiner's recommendation, Applicant has amended claim 18 to recite an isolated nucleic acid molecule in which the capsid protein is HaSV stunt virus P71 (SEQ ID NO: 50).

Claim 21 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite because the metes and bounds of an "antisense sequence" and a mimicking structure are not clear. Applicant has amended claim 21 to delete the term "mimicking sequence." Applicant further directs the Examiner's attention to page 116, lines 3-10 in which the antisense sequences of the present invention are defined as RNA secondary structures which have the ability to cause toxicity to cells (e.g., prevention of the expression of key cellular enzymes as described in Eguchi, Y., Itoh, T., and Tomizawa, J. (1991). Antisense sequences are commonly known and recognized in the art as capable of hybridizing to specific cellular mRNAs. Moreover, Claim 15, from which claim 21 depends, recites that second sequences may be insecticidal or may

Serial No.: 09/677,653
Filing Date: October 3, 2000

encode an insecticidal protein toxin. For the foregoing reasons, Applicant requests withdrawal of the outstanding rejection.

Claim Rejections – 35 U.S.C. §112, First Paragraph, Written Description

Claim 15 (and claims 21-22 which depend therefrom) is rejected under 35 U.S.C. §112, first paragraph, on the grounds that the written description fails to describe the nucleic acids which incorporate insecticidal sequences, antisense sequences, and mimicking structures. As stated previously, claim 21 has been amended to delete the term mimicking structure. In addition, the present invention teaches nucleic acid sequences which encode capsid proteins of an insect small RNA virus in which the capsid proteins are operative for delivering second sequences to insects (e.g., which may be either insecticidal or which encode an insecticidal toxin). The nucleic acid molecules recited in claim 15, therefore, may be used to deliver any nucleic acid sequence which ultimately produces a detrimental effect upon an insect. The second sequence may be insecticidal (e.g., a ribozyme, DNAzyme, or an antisense sequence) or may, alternatively, encode a protein which is insecticidal or which produces a detrimental effect upon the insect. Accordingly, the invention may be practiced to deliver essentially any nucleic acid sequence to an insect. The invention may, for example, be used for the delivery of nucleic acids which encode GFP (green fluorescent protein) for expression of GFP in insect hosts. Since a specific utility of the invention is the control of insect populations, however, the claims recite sequences which are either insecticidal or which encode toxins which are insecticidal.

For the foregoing reasons, the specification provides adequate descriptions of the insecticidal and antisense sequences recited in the claims. Applicant accordingly respectfully requests withdrawal of the outstanding rejection of Claims 15 (and claims 21-22 which depend therefrom) under 35 U.S.C. §112, first paragraph.

Serial No.: 09/677,653
Filing Date: October 3, 2000

Claim Rejections – 35 U.S.C. §112, First Paragraph, Enablement

Claim 15 (and claims 16-23 which depend therefrom) are rejected under 35 U.S.C. §112, first paragraph, for lacking enablement. In particular, the Examiner states that while the specification is enabling for isolated nucleic acid sequences comprising a first sequence encoding a capsid protein of an insect RNA virus and a second sequence encoding an insecticidal protein toxin or ribozyme, the specification does not reasonably provide enablement for nucleic acids which encode antisense sequences or mimicking structures. As previously stated, claim 21 has been amended to delete the term mimicking structure. The skilled artisan is further aware that ribozymes are catalytic forms of antisense sequences. Both antisense sequences and ribozymes hybridize to target mRNA molecules for the inhibition of gene expression. Ribozymes, in addition to binding target mRNA, directly cleave ribonucleic acid. Accordingly, the nucleic acids recited in the claims (e.g., having a second sequence encoding an “antisense sequence”) can readily be produced by the skilled artisan without undue experimentation. As indicated herein, the nucleic acids of the present invention may be used to deliver any functional nucleic acid (e.g., a nucleic acid sequence which is insecticidal *per se* or a nucleic acid which encodes an insecticidal toxin), to an insect host. The construction of nucleic acids in which the second sequence is an antisense sequence is, moreover, provided in the specification and in the Examples (e.g., see page 82, lines 20-30). The specification further provides that selected genes may be placed under the control of *Helicoverpa armigera* replication or encapsidation signals using standard techniques in molecular biology (see e.g., page 83, lines 1-5 and 29-31 and page 84, lines 1-2). Given the present disclosure, the skilled artisan can readily appreciate that any selected nucleic acid (e.g., antisense or otherwise) can be delivered to an insect host using the nucleic acid molecule that is recited in claim 15.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech Inc. v.

Serial No.: 09/677,653
Filing Date: October 3, 2000

Monoclonal Antibodies, Inc. 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicant maintains that this burden has been met and accordingly requests withdrawal of the outstanding enablement rejection under 35 U.S.C. §112, first paragraph.

Priority

The Examiner argues that patent application 08/089,372, filed July 8, 1993, now abandoned, provides no support for the claimed subject matter in the instant application and accordingly, the pending claims are not entitled to a priority date of July 8, 1993. Applicant directs the Examiner's attention to page 10, lines 31-67 and page 11, lines 1-3 (e.g., which correspond to later filed WO 94/04660 page 12, lines 21-24, cited by the Examiner as prior art against the present application). Applicant further directs the Examiner's attention to page 16, lines 13-22 (e.g., which corresponds to WO 94/04660 page 18, lines 4-12) and page 68, lines 23-67 and page 69, line 1 (e.g., which corresponds to WO 94/04660 page 70, lines 10-19).

Applicant further directs the Examiner's attention to page 16, lines 24-67; page 17, line 1; page 70, lines 23-67 and page 71, line 18, as well as to Figs. 14b, 15 and 16 of patent application 08/089,372. Applicant maintains that the sections of patent application 08/089,372 recited herein support the claimed subject matter of the present invention and additionally correspond to sections of later filed issued patent WO 94/04660, which has been cited by the Examiner as prior art against the present application. Accordingly, the priority date of the claimed subject matter of the instant application, is at least July 8, 1993.

Claim Rejections – 35 U.S.C. §102(b) – *Christian et al.* (WO 94/04660)

Claim 15 (and dependent claims 16-23) are rejected under 35 U.S.C. §102(b) as being anticipated by *Christian et al.*

Serial No.: 09/677,653
Filing Date: October 3, 2000

Christian et al. discloses fusion proteins of P71 and HaSV polypeptides or proteins which exhibit insecticidal activity or provide target specificity for insecticidal agents (*see e.g.*, page 12, lines 21-27). The reference further discloses RNA 2 HaSV viral genome wherein a toxin or reporter gene is fused to the initiation codon of P71 (*see e.g.*, page 71, lines 19-21).

As discussed herein, the claimed subject matter of the present invention has a priority date of at least July 8, 1993. Accordingly, *Christian et al.* WO 94/04660, having a filing date March 3, 1994, cannot meritoriously be cited as prior art against Applicant under 35 U.S.C. §102(b).

Claim Rejections – 35 U.S.C. §103(a) – *Wilcox, et al.* in view of *Hanzlik, et al.* (1993)

Claim 15 (and dependent claims 16-23) are rejected under 35 U.S.C. §103(a) as being anticipated by *Wilcox, et al.* in view of *Hanzlik, et al.* (1993).

Wilcox, et al. teaches insecticidal fusion proteins expressed as polypeptide products of a hybrid gene comprising a cytoxic agent (*e.g.*, a ribosome inactivator such as ricin) and a specific insect gut cell recognition (“binding”) protein wherein the gut cell recognition protein directs the cytotoxic agents to the host targets (*see e.g.*, column 1, lines 44-49 and column 3, line 27).

Hanzlik, et al. (1993) discloses *Helicoverpa amerigera* stunt virus capsid proteins of molecular weight 70K, 65K and 6K (page 1807).

Applicant respectfully traverses the rejection.

As discussed herein, the claimed subject matter of the present invention has a priority date of at least July 8, 1993. Accordingly, neither the subject matter of *Hanzlik, et al.*, having a publication date of September, 1993, nor the subject matter of *Wilcox, et al.*, having a filing date May 10, 1995, can meritoriously be cited as prior art against Applicant under 35 U.S.C. §103(a). Applicant therefore respectfully requests withdrawal of the outstanding rejection.

Serial No.: 09/677,653
Filing Date: October 3, 2000

Claim Rejections – 35 U.S.C. §103(a) – *Wilcox, et al.* in view of *Hanzlik, et al.* (1993) and *Hanzlik, et al.* (1995)

Claim 18 is rejected under 35 U.S.C. §103(a) as being anticipated by *Wilcox, et al.* in view of *Hanzlik, et al.* (1993) and *Hanzlik, et al.* (1993).

Wilcox, et al. and *Hanzlik, et al.* (1993) are discussed herein. *Hanzlik, et al.* (1995) teaches an open reading frame which encodes the *Helicoverpa armigera* 71kDa precursor (P71) which, when cleaved at the Asn-Phe site, produces capsid proteins 64 kDa and 7kDa.

Applicant respectfully traverses the rejection.

As recited herein, the claimed subject matter of the present invention has a priority date of at least July 8, 1993. Accordingly, neither the subject matter of *Hanzlik, et al.*, having a publication date of September, 1993, the subject matter of *Hanzlik, et al.*, having a publication date of April 1995, nor the subject matter of *Wilcox, et al.* having a filing date May 10, 1995, can meritoriously be cited as prior art against Applicant under 35 U.S.C. §103(a). Applicant therefore respectfully requests withdrawal of the outstanding rejection.

Claim Rejections – 35 U.S.C. §103(a) – *Wilcox, et al.* in view of *Harley, et al.*

Claim 15 (and claims 16 and 19-23 which depend therefrom) is rejected under 35 U.S.C. §103(a) as being anticipated by *Wilcox, et al.* in view of *Harley, et al.*

Wilcox, et al. is discussed herein. *Harley, et al.* teaches a cytoplasmic RNA virus which infects *Helicoverpa armigera*.

Applicant respectfully traverses the rejection.

As discussed herein, the claimed subject matter of the present invention has a priority date of at least July 8, 1993. Accordingly, the subject matter of *Wilcox, et al.*, having a filing date of May 10, 1995 cannot meritoriously be cited as prior art against Applicant under 35 U.S.C. §103(a). Since *Wilcox* is the primary reference under the present 35 U.S.C. §103(a) rejection, it is submitted that the secondary reference (e.g., *Harley, et al.*) does not render the

Serial No.: 09/677,653
Filing Date: October 3, 2000

claims unpatentable. Applicant accordingly respectfully requests withdrawal of the outstanding rejection.

CONCLUSION

Applicants submit that the claims are now in condition for allowance. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: December 6, 2002



Richard F. Trecartin, Reg. No. 31,801

Four Embarcadero Center, Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989
#1090793

Serial No.: 09/677,653
Filing Date: October 3, 2000

VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph beginning at page 1, line 2, with the following rewritten paragraph:

----This application is a divisional of U.S. Application Serial Number 08/485,355, filed June 7, 1995, now U.S. Patent No. 6,177,075, which is a continuation-in-part of U.S. Application Serial Number 08/440,522, filed May 12, 1995, abandoned, which is a continuation-in-part of U.S. Application Serial Number 08/089,372, filed July 8, 1993, abandoned.--

Please replace the paragraph beginning at page 277, line 1, with the following rewritten paragraph:

--WHAT IS CLAIMED IS:--

In the Claims:

17. (Amended) An isolated nucleic acid molecule as claimed in claim 15 in which the insect small RNA virus is Helicoverpa armigera stunt virus (HaSV).

18. (Amended) An isolated nucleic acid molecule as claimed in claim 15 in which the capsid protein is HaSV P71 (SEQ ID [No.] NO: 50).

21. (Amended) An isolated nucleic acid molecule as claimed in claim 15 in which the second sequence is an antisense sequence [,] or a ribozyme [or a mimicking structure].

22. (Amended) An isolated nucleic acid molecule as claimed in claim 21 in which the [mimicking structure] second sequence is double stranded RNA.

Serial No.: 09/677,653
Filing Date: October 3, 2000

Pending Claims 15-23, as Amended

15. An isolated nucleic acid molecule comprising a first sequence encoding at least one capsid protein of an insect small RNA virus and a second sequence which is insecticidal or which encodes an insecticidal protein toxin.

16. An isolated nucleic acid molecule as claimed in claim 15 in which the nucleic acid is RNA.

17. (Amended) An isolated nucleic acid molecule as claimed in claim 15 in which the insect small RNA virus is Helicoverpa armigera stunt virus (HaSV).

18. (Amended) An isolated nucleic acid molecule as claimed in claim 15 in which the capsid protein is HaSV P71 (SEQ ID NO: 50).

19. An isolated nucleic acid molecule as claimed in claim 15 in which the insecticidal toxin is of plant origin.

20. An isolated nucleic acid molecule as claimed in claim 15 in which the insecticidal toxin is Ricin A.

21. (Amended) An isolated nucleic acid molecule as claimed in claim 15 in which the second sequence is an antisense sequence or a ribozyme.

22. (Amended) An isolated nucleic acid molecule as claimed in claim 21 in which the second sequence is double stranded RNA.

23. An isolated nucleic acid molecule as claimed in claim 15 in which the insecticidal toxin is less toxic to plants than insects.

24. (Withdrawn) A transgenic plant having introduced into its genome the nucleic acid of claim 15.